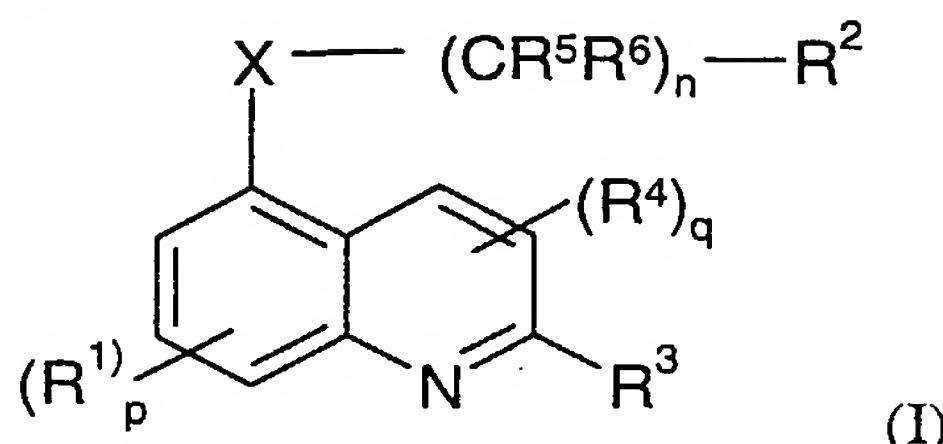


CLAIMS

1. A compound of formula



5 or a pharmaceutically acceptable salt or solvate thereof, wherein

p is 0, 1 or 2;

each R¹ independently represents halogen or C₁-C₆ alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy;

X is C(O)NH or NHC(O);

10 n is 1, 2, 3, 4 or 5;

within each grouping, CR⁵R⁶, R⁵ and R⁶ each independently represent hydrogen, halogen, phenyl or C₁-C₆ alkyl, or R⁵ and R⁶ together with the carbon atom to which they are both attached form a C₃-C₈ cycloalkyl ring;

R^2 represents an unsaturated 4- to 10-membered ring system which may comprise at

15 least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system

being optionally substituted with at least one substituent selected from halogen, -COOR¹³, hydroxyl, -NR¹⁴R¹⁵, -CONR¹⁶R¹⁷, -SO₂NR¹⁸R¹⁹, -NR²⁰SO₂R²¹, C₁-C₆ alkyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkoxy, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkoxy carbonyl, C₁-C₆ hydroxalkyl and -S(O)_mC₁-C₆ alkyl where m is 0, 1 or 2;

20 R³ represents hydrogen or a group -R⁷, -OR⁷, -SR⁷ or -NR⁷R⁸;

q is 0, 1 or 2;

each R⁴ independently represents halogen or C₁-C₆ alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy;

R^7 and R^8 each independently represent hydrogen, C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl

25 or a saturated or unsaturated 3- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the alkyl, cycloalkyl and heterocyclic ring system each being optionally substituted with at least one substituent

selected from halogen, hydroxyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ hydroxyalkyl, C₁-C₆ hydroxyalkoxy, C₁-C₆ alkoxycarbonyl, C₃-C₈ cycloalkyl, -NR⁹R¹⁰, -COOR²², -CONR²³R²⁴, -SO₂NR²⁵R²⁶, -NR²⁷SO₂R²⁸ and ZR⁶⁸ or

alternatively, R⁷ and R⁸ may together with the nitrogen atom to which they are

5 attached from a 4- to 7-membered saturated heterocyclic ring that optionally further comprises one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur and that optionally further comprises a bridging group, the heterocyclic ring being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ hydroxyalkyl, C₁-C₆ hydroxyalkoxy, C₁-C₆ alkoxycarbonyl, C₃-C₈ cycloalkyl, -NR¹¹R¹², -COOR²⁹, -CONR³⁰R³¹, -SO₂NR³²R³³, -NR³⁴SO₂R³⁵, Z'R⁶⁹, (CH₂)₁₋₆NR⁷⁰R⁷¹, SO₂R⁷², NR⁷³CONR⁷⁴SO₂R⁷⁵ or M(CH₂)₁₋₆COOR⁷⁶ wherein M represents a bond, O, S, SO, SO₂, and a group >NR⁷⁷;

R⁹ and R¹⁰ each independently represent hydrogen or a C₁-C₆ alkylcarbonyl,

15 C₂-C₇ alkenyl or C₁-C₇ alkyl group, each group being optionally substituted with at least one substituent selected from hydroxyl, -NR³⁶R³⁷, -COOR³⁸, -CONR³⁹R⁴⁰, -SO₂NR⁴¹R⁴², -NR⁴³SO₂R⁴⁴, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkoxycarbonyl and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system in turn being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo, carboxyl, cyano, C₁-C₆ alkyl and C₁-C₆ hydroxyalkyl, or

20 alternatively, R⁹ and R¹⁰ may together with the nitrogen atom to which they are

attached from a 4- to 7-membered saturated heterocyclic ring that optionally further comprises one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the heterocyclic ring being optionally substituted with at least one substituent selected from -OR⁵⁴, -NR⁵⁵R⁵⁶, -(CH₂)_t-NR⁵⁷R⁵⁸ where t is 1, 2, 3, 4, 5 or 6, -COOR⁵⁹, -CONR⁶⁰R⁶¹, -SO₂NR⁶²R⁶³, -NR⁶⁴SO₂R⁶⁵, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkoxycarbonyl and Z''R⁸⁰;

25 R¹¹ and R¹² each independently represent hydrogen or a C₁-C₆ alkylcarbonyl, C₁-

30 C₆ alkoxycarbonyl, C₂-C₇ alkenyl or C₁-C₇ alkyl group, each group being optionally

substituted with at least one substituent selected from hydroxyl, -NR⁴⁵R⁴⁶, -COOR⁴⁷, -CONR⁴⁸R⁴⁹, -SO₂NR⁵⁰R⁵¹, -NR⁵²SO₂R⁵³, -NR⁶⁶C(O)R⁶⁷, C₁-C₆ alkoxy, C₁-C₆ alkylthio and C₁-C₆ alcoxycarbonyl;

Z, Z' and Z'' independently represent a bond, O, S, SO, SO₂, >NR⁷⁸, C₁₋₆ alkylene,

5 or a group -O(CH₂)₁₋₆, -NR⁷⁹(CH₂)₁₋₆- or -S(O)_p(CH₂)₁₋₆- wherein p is 0, 1 or 2;

R⁶⁸, R⁶⁹ and R⁸⁰ independently represent tetrazolyl or a 5- to 6- membered

heterocyclic ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which heterocyclic ring is substituted by at least one substituent selected from hydroxyl, =O, and =S, and which heterocyclic ring may further be optionally substituted

10 by at least one substituent selected from halogen, nitro, cyano, -SO₂C₁₋₆ alkyl, C₁₋₆ alcoxycarbonyl, and a C₁₋₆ alkyl group which C₁₋₆ alkyl group can be optionally substituted by at least one substituent selected from halogen and hydroxyl;

R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ each independently represent hydrogen or C₁-C₆ alkyl optionally substituted by at least one substituent selected from hydroxyl,

15 halogen and C₁-C₆ alkoxy;

R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R³⁴ and R³⁵ each

independently represent hydrogen or C₁-C₆ alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy;

R³⁶, R³⁷, R³⁸, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵¹, R⁵²

20 and R⁵³ each independently represent hydrogen or C₁-C₆ alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy;

R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶⁰, R⁶¹, R⁶², R⁶³, R⁶⁴, R⁶⁵, R⁶⁶ and R⁶⁷ each

independently represent hydrogen or C₁-C₆ alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy; and

25 R⁷⁰, R⁷¹, R⁷², R⁷³, R⁷⁴, R⁷⁵, R⁷⁶, R⁷⁷, R⁷⁸ and R⁷⁹ each independently represent hydrogen or C₁-C₆ alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy;

with the provisos that:

(a) when X represents NHC(O), p is 0, q is 0, n is 1 and R³, R⁵ and R⁶ each independently represent hydrogen, then R² is other than a 2-carboxy-phenyl group; and

5 (b) when X represents NHC(O), p is 0, q is 0, n is 2, R³ represents hydrogen and each R⁵ and R⁶ independently represents hydrogen, then R² is other than a 3,4-diamino-phenyl group or a 5-methyl-2-furanyl group; and

10 (c) when X represents C(O)NH, p is 0, q is 0, n is 2, R³ represents hydrogen and each R⁵ and R⁶ independently represents hydrogen, then R² is other than an unsubstituted phenyl group, an unsubstituted 1H-indol-3-yl group, or a 2-methyl-1H-indol-3-yl group.

2. A compound according to claim 1, wherein X is NHC(O).

3. A compound according to claim 1 or claim 2, wherein R² represents an unsaturated 4-, 5- or 6-membered ring optionally comprising one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted with one, two, three or four substituents independently selected from halogen, -COOR¹³, hydroxyl, -NR¹⁴R¹⁵, -CONR¹⁶R¹⁷, -SO₂NR¹⁸R¹⁹, -NR²⁰SO₂R²¹, C₁-C₄ alkyl, C₁-C₄ alkylcarbonyl, C₁-C₄ alkoxy, C₁-C₄ alkylcarbonyloxy, C₁-C₄ alkoxycarbonyl, C₁-C₄ hydroxyalkyl and -S(O)_mC₁-C₄ alkyl where m is 0, 1 or 2.

4. A compound according to any one of the preceding claims, wherein R³ represents hydrogen or a group -R⁷ or -NR⁷R⁸.

25 5. A compound according to any one of the preceding claims wherein R⁷ and R⁸ each independently represent hydrogen or C₁-C₁₀ alkyl optionally substituted with one or two substituents independently selected from halogen, hydroxyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ hydroxyalkyl, C₁-C₄ hydroxyalkoxy, C₁-C₄ alkoxycarbonyl, C₅-C₆ cycloalkyl, -NR⁹R¹⁰, -COOR²², -CONR²³R²⁴, -SO₂NR²⁵R²⁶ and 30 -NR²⁷SO₂R²⁸.

6. A compound according to any one of claims 1 to 4, wherein R⁷ and R⁸ together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen atom, the heterocyclic ring being optionally substituted with one or two substituents independently selected from halogen, hydroxyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ hydroxyalkyl, C₁-C₄ hydroxyalkoxy, C₁-C₄ alcoxycarbonyl, C₅-C₆ cycloalkyl, -NR¹¹R¹², -COOR²⁹, -CONR³⁰R³¹, -SO₂NR³²R³³ and -NR³⁴SO₂R³⁵.

10 7. A compound according to any one of the preceding claims, wherein within each grouping CR⁵R⁶, R⁵ and R⁶ each independently represent hydrogen or C₁-C₄ alkyl.

8. A compound according to claim 1 selected from:

6-Chloro-2-methyl-N-[(2*R*)-2-phenylpropyl]-5-quinolinecarboxamide,

15 6-Chloro-2-methyl-N-[(2*S*)-2-phenylpropyl]-5-quinolinecarboxamide,

(*βR*)-N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-*β*-methylbenzenepropanamide,

(*βR*)-N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-*β*-methyl-benzenepropanamide,

6-Chloro-2-methyl-N-(2-phenylethyl)-5-quinolinecarboxamide,

20 (*βR*)-N-[6-Chloro-2-[3-(ethylamino)propyl]-5-quinolinyl]-*β*-methylbenzenepropanamide,

(*βR*)-N-[6-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-5-quinolinyl]-*β*-methylbenzenepropanamide,

3,4-Dichloro-*α*-methyl-N-5-quinolinyl-benzenepropanamide,

25 (*βR*)-N-[6-Chloro-2-[(2-[(2-hydroxyethyl)amino]ethyl]amino]-5-quinolinyl]-*β*-methylbenzenepropanamide,

2-Chloro-N-[6-chloro-2-(1-piperazinyl)-5-quinolinyl]-benzenepropanamide,

2,4-Dichloro-N-[6-chloro-2-(1-piperazinyl)-5-quinolinyl]-benzenepropanamide,

4-Chloro-N-[6-chloro-2-(1-piperazinyl)-5-quinolinyl]-benzenepropanamide,

(βR)-*N*-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]- β -methylbenzenepropanamide,

N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-2-methoxy-benzenepropanamide,

(βR)-*N*-[6-Chloro-2-[(3*S*)-3-[(3-hydroxypropyl)amino]-1-pyrrolidinyl]-5-quinolinyl]- β -methylbenzenepropanamide,

(βR)-*N*-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]- β -methylbenzenepropanamide,

N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-benzenepropanamide,

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-2-chloro-

10 benzenepropanamide,

2-Chloro-*N*-[6-chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-benzenepropanamide,

1-[6-Chloro-5-[[3-(2-chlorophenyl)-1-oxopropyl]amino]-2-quinolinyl]-4-piperidinecarboxylic acid,

15 2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-*N*-[2-(2-chlorophenyl)ethyl]-5-quinolinecarboxamide,

6-Chloro-*N*-[2-(2-chlorophenyl)ethyl]-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinecarboxamide,

20 1-[6-Chloro-5-[[[2-(2,6-dichlorophenyl)ethyl]amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid,

1-[6-Chloro-5-[[[2-(2-chlorophenyl)ethyl]amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid,

1-[6-Chloro-5-[[[(2,2-diphenylethyl)amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid,

25 1-[6-Chloro-5-[[[(2-phenylethyl)amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid,

1-[6-Chloro-5-[[[2-(2-fluorophenyl)ethyl]amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid,

30 1-[6-Chloro-5-[[[2-(2-methylphenyl)ethyl]amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid,

1-[6-Chloro-5-[[[(2*S*)-2-phenylpropyl]amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid,

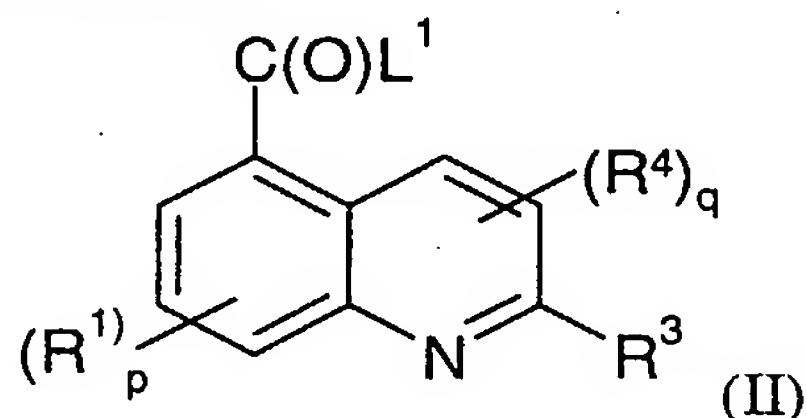
6-Chloro-*N*-[2-(2-chlorophenyl)ethyl]-2-[4-(1,5-dihydro-5-oxo-4*H*-1,2,4-triazol-4-yl)-1-piperidinyl]-5-quinolinecarboxamide, and

5 1-[6-Chloro-5-[[[2-(4-chlorophenyl)ethyl]amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid,

and all their pharmaceutically acceptable salts and solvates.

10 9. A process for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, which comprises

(a) reacting a compound of formula

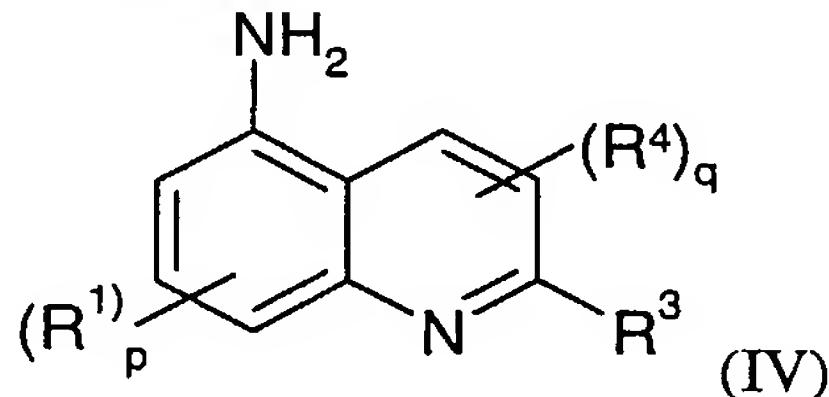


15 wherein L¹ represents a leaving group (e.g. hydroxyl or halogen) and p, q, R¹, R³ and R⁴ are as defined in formula (I), with a compound of formula



wherein n, R², R⁵ and R⁶ are as defined in formula (I); or

20 (b) reacting a compound of formula

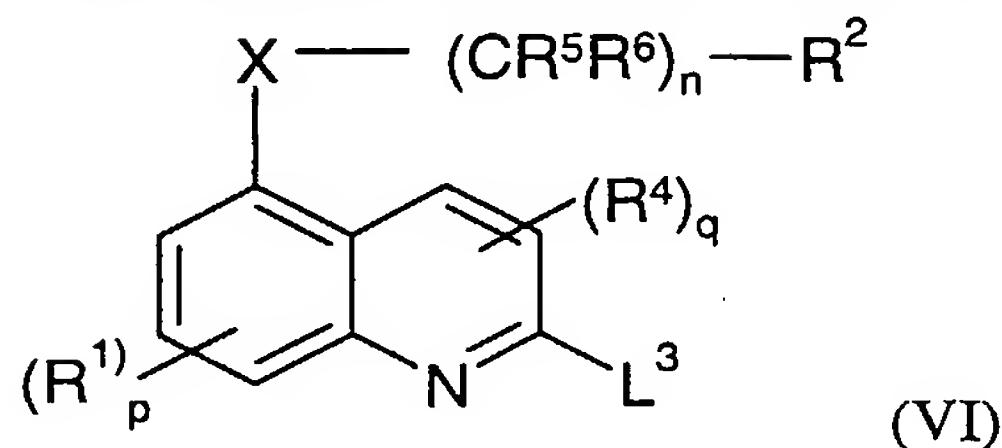


wherein p, q, R¹, R³ and R⁴ are as defined in formula (I), with a compound of formula



25 wherein L² represents a leaving group (e.g. hydroxyl or halogen) and n, R², R⁵ and R⁶ are as defined in formula (I); or

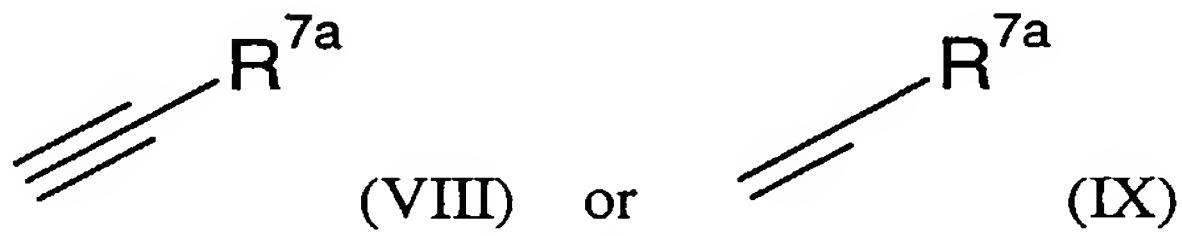
(c) when R³ represents a group -NR⁷R⁸, reacting a compound of formula



wherein L³ is a leaving group (e.g. chloride, bromide, fluoride, iodide,

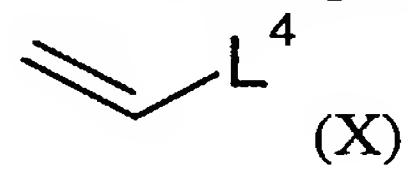
5 paratoluenesulphonate or methanesulphonate) and n, p, q, X, R¹, R², R⁴, R⁵ and R⁶ are as defined in formula (I), with a compound of formula (VII), H-NR⁷R⁸, wherein R⁷ and R⁸ are as defined in formula (I); or

10 (d) when R³ represents a group R⁷ where R⁷ is an optionally substituted C₃-C₁₀ alkyl group, reacting a compound of formula (VI) as defined in (c) above with a compound of formula



wherein R^{7a} represents a C₁-C₈ alkyl group optionally substituted as defined for R⁷ in formula (I), optionally followed by a hydrogenation reaction; or

15 (e) when R³ represents a group R⁷ where R⁷ is -(CH₂)₂NR⁹R¹⁰, reacting a compound of formula (VI) as defined in (c) above with a compound of formula

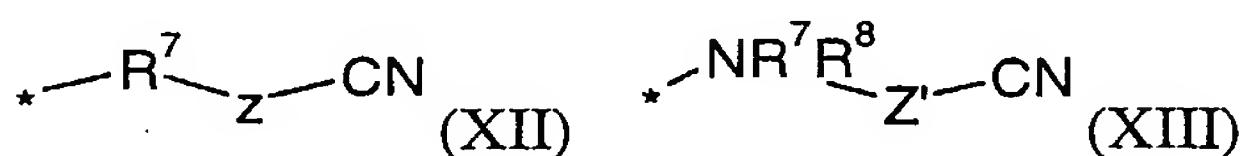


wherein L⁴ is a leaving group (eg. trialkyltin, dialkylboron or zinc), followed by reaction 20 with a compound of formula (XI), HNR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined in formula (I); or

(f) when R³ represents a group R⁷ where R⁷ is -CH₂NR⁹R¹⁰, reacting a compound of formula (VI) as defined in (c) above with a compound of formula (X) as defined in (e)

above, followed by an oxidation reaction and then by reaction with a compound of formula (XI) as defined in (e) above under reductive amination conditions; or

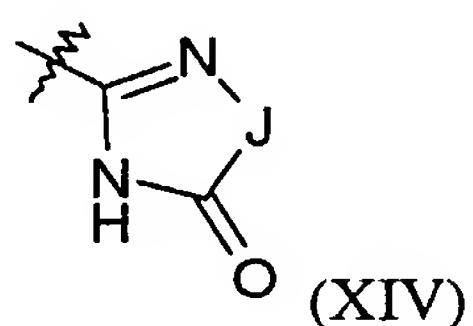
(g) when R^3 represents a group R^7ZR^{68} or NR^7R^8 wherein R^7 and/or R^8 are substituted by a group $Z'R^{69}$ or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring substituted by a group $Z'R^{69}$, and R^{68} or R^{69} is tetrazolyl, reacting a group of formula (XII) or (XIII)



10

with a compound of formula GN_3 , wherein G is sodium, a trialkylsilyl, an alkyltin or ammonium, to yield a group of formula I wherein R^7 , R^8 , Z, Z' are as defined in formula (I); or

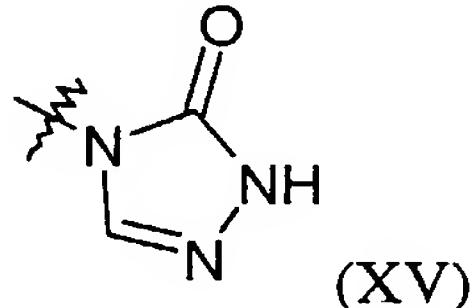
15 (h) when R^3 represents a group R^7ZR^{68} or NR^7R^8 wherein R^7 and/or R^8 are substituted by a group $Z'R^{69}$ or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring substituted by a group $Z'R^{69}$, and R^{68} or R^{69} is group of formula



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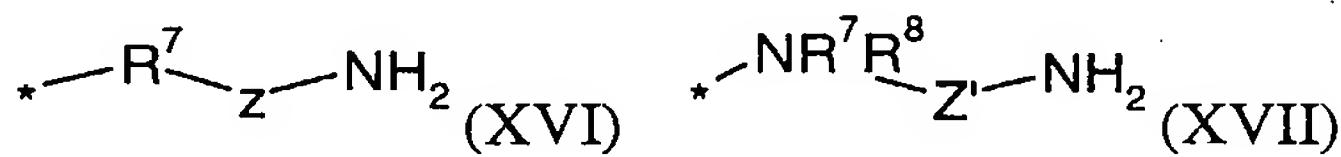
reacting a compound of formula XII or XIII wherein XII or XIII are as defined in (g) above with hydroxylamine, followed by treatment with 1,1'-thiocarbonyldiimidazole and subsequent treatment with silica gives a group of formula (XIV) wherein J is S, alternatively reacting a compound of formula XII or XIII wherein XII or XIII are as defined in (g) above with hydroxylamine, followed by treatment with a suitable chloroformate gives a group of formula (XIV) wherein J is O; or

(i) when R³ represents a group R⁷ZR⁶⁸ or NR⁷R⁸ wherein R⁷ and/or R⁸ are substituted by a group Z'R⁶⁹ or R⁷ and R⁸ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring substituted by a group Z'R⁶⁹, and R⁶⁸ or R⁶⁹ is



5

reacting a compound of formula XVI or XVII



with a source of phosgene followed by treatment with formyl hydrazine and subsequent 10 treatment with base;

and optionally after (a), (b), (c), (d), (e), (f), (g), (h) or (i) carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt or solvate of the compound.

15

10. A compound of formula (VI) as defined in claim 9.

11. (βR)-N-(2,6-Dichloro-5-quinolinyl)- β -methyl-benzenepropanamide.

20 12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

25 13. A process for the preparation of a pharmaceutical composition as claimed in claim 12 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in any one of claims 1 to 8 with a pharmaceutically acceptable adjuvant, diluent or carrier.

14. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 for use in therapy.

5 15. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

10 16. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in the treatment of an obstructive airways disease.

17. Use according to claim 16, wherein the obstructive airways disease is asthma or chronic obstructive pulmonary disease.

15 18. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in the treatment of osteoarthritis.

20 19. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in the treatment of atherosclerosis.

25 20. A method of treating rheumatoid arthritis or osteoarthritis which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8.

21. A method of treating an obstructive airways disease which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8.